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In re application of

Peter FISCHER

Serial No. 09/856,352

Filed October 17, 2001

USE OF EFFECTORS OF CENTRAL

CHOLINERGAC NERVOUS SYSTEM FOR

THE TREATMENT OF DELIRIUM

Confirmation No. 6840

GROUP 1614

Examiner Vicki Y. Kim

DECLARATION UNDER RULE 132

Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Peter Fischer, M.D., Ph.D., hereby declare as follows:

I am the inventor of the above-identified applicaition. I make this declaration in support of the present application, and to provide evidence in rebuttal of the contention in the Official Action of March 13, 2003, that the claimed invention is anticiapted and/or obvious in view of the cited Rupreht et al abstract (1990).

Anticholinergic delirium is defined as a delirium which occurs when anticholinergically acting substances are administered. An unusual name of anticholinergic delirium is "central anticholinergic syndrome" as used by Rupreht et al (1990). As stated in the abstract, "it occurs when central cholinergic sites are occupied by specific drugs and also as a result of an insufficient release of acetylcholine". An example of a drug occupying

central cholinergic sites is atropine sulphate, examples of drugs which act anticholinergically by other ways are benzodiazepines, ketamine, or halogenated anaesthetic agents like halothane or influrane. All these substances are anticholinergics, i.e. drugs with central anticholinergic activity, as described in the review article "Postoperative delirium in the elderly" by O'Keefe ST & Chonchubhair AN, in the British Journal of Anaesthesia 1994;73:673-687. In this article the anesthetics mentioned above are listed in Table 6 as "drugs with central anticholinergic activity". Table 5 lists a lot of other causes of postoperative delirium in the elderly. Table 6 also lists other drugs capable to inducing non-anticholinergic delirium. Postoperative delirium can, thus, be classified into anticholinergically induced delirium and otherwise caused delirium (that is non-anticholinergically induced delirium).

Anticholinergically induced delirium can be treated by cholinomimetic agents like physostigmin. This has been previously discussed. For example, the Examiner's attention is respectfully directed to the above-identified reference on page 683 (first paragraph). However, the present invention provides that non-anticholinergically caused deliria, and postoperative deliria in particular (i.e. excluding those induced by anticholinergics), either improve following administration of cholinomimetic drugs called acetylcholinesterase-inhibitors or can be effectively prevented by the use of acetylcholinesterase-inhibitors. That has never been described elsewhere and no acetylcholinesterase-inhibitor currently used to treat degenerative brain disease (Alzheimer's disease, Lewy Body dementia, vascular dementia, mixed dementia) has been used to act in non-anticholinergic delirium and non-anticholinergic postoperative delirium, especially. The cited reference includes recommendations for pharmacological treatment of postoperative delirium (pp. 682 f.) and mentiones neuroleptics, benzodiazepines, and chlormethiazole. Physiostigmine is desribed to specifically reverse delirium caused by anticholinergic agents (p.683, 1st paragraph).

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Peter Fischer, M.D., Ph.D

Sept 11th, 2003

Date

British Journal of Anaesthesia 1994; 73: 673–687

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REVIEW ARTICLE

Postoperative delirium in the elderly

S. T. O'KEEFFE AND Á. NÍ CHONCHUBHAIR

Delirium, an acute mental syndrome caused by organic factors, is a common complication of surgery in elderly people [165, 172], but it has attracted little attention until recently and is often unrecognized or misdiagnosed by medical staff [12, 117]. Apart from its frequency, there are several reasons why this syndrome is important in the older surgical patient. Delirium is often the presenting feature of physical illness or drug toxicity [105, 111] and failure to ppreciate this may lead to delay in diagnosing and treating the underlying cause. Complications of immobility and of sedation, such as decubitus ulcers and chest infections, are common in patients with prolonged delirium [10, 55, 167]. Delirium may cause considerable distress and agitation, and there is a high risk of self injury [14, 90, 176]. Economic implications include the need for extra nursing care, increased duration of hospital stay and a high rate of discharge to long-term care [100, 159].

The diagnosis, investigation and treatment of postoperative delirium in the elderly are important to many specialties and discussion of these topics is widely dispersed in the literature. The aim of this article is to review the current state of knowledge of delirium and to determine areas requiring further research.

Terminology

Postoperative delirium has been recognized for centuries [93], yet there is still a paucity of good data on its incidence and natural history. One major problem is the terminological chaos which has bedevilled this subject: terms used previously to describe delirium include "acute confusional state", "acute brain failure", "organic brain syndrome" and "toxic psychosis" [96]. Although patients are often described as "confused" by lay people and health professionals, there is no common understanding or standard definition for this word, and to many "confusion" implies an irreversible, untreatable condition [149].

The diagnosis of delirium and the ability of researchers to communicate with one another have been improved by the development of specific diagnostic criteria by the American Psychiatric Association in the *Diagnostic and Statistical Manual*, third edition (DSM-3) in 1980 [4] (table 1), and in a 1987 revision (DSM-3-R) [5]. "Delirium" is now the appropriate term for an organic brain syndrome which develops acutely, has a fluctuating clinical course and is characterized by disturbances of attention, memory, orientation, perception, psychomotor behaviour and sleep.

"Emergence" and "interval" delirium

Lipowski has distinguished between "emergence" delirium, which develops within the first 24 h after surgery, and "interval" delirium, which occurs after a lucid interval of 1 or more days [93]. However, there is no consensus on this terminology in the literature. On the basis of her study of post-cardiotomy delirium, Sadler suggested that the difference between immediate and delayed delirium is artificial [136]. Some authors ignore symptoms which are present only during the first 8 h after surgery when diagnosing delirium [11], while others include symptoms which develop after a lucid period of any duration [61]. Emergence is often applied only to mental disturbances which appear at the very onset of the postoperative course: "emergence excitement" refers to transient restlessness or agitation [8, 24, 36] and "emergence somnolence" to delayed recovery of cognitive function or prolonged

Table 1 Diagnostic criteria for delirium (adapted from DSM-3 criteria [18])

Reduced clarity of awareness of the environment with reduced capacity to shift, focus and sustain attention to environmental stimuli
At least two of the following:
Perceptual disturbances
Incoherent speech
Disturbed sleep–wake cycle
Increased or decreased psychomotor activity
Disorientation and memory impairment
Clinical features that develop over hours to days and tend to fluctuate over the course of 1 day
Evidence of a specific organic factor judged to be aetiologically significant (often only identified retrospectively)

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Key words

Psychological responses, postoperative. Recovery, postoperative. Anaesthesia, geriatric.

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coma after anaesthesia [60, 135]. Anticholinergic drugs are often responsible for disturbed recovery from anaesthesia and "central anticholinergic syndrome" can be applied when this aetiology is proved [135]. However, as other causes can produce an identical clinical picture, it is usually preferable to use a descriptive term rather than one which implies a single, specific aetiological factor. In this article, delirium refers to interval delirium unless otherwise stated.

Clinical features

Delirium usually develops during the first 4 days after surgery [14, 110, 111]. It is often recognized first at night when a patient is found to be agitated and disoriented. A prodromal phase can be identified in many patients [110]. During this period, patients appear irritable, perplexed or withdrawn and may be evasive or angry at attempts to perform cognitive testing.

Impaired attentiveness is now regarded as the central feature of delirium [92]. The patient is highly distractible and is unable to direct, sustain or shift attention appropriately. Questions often need to be repeated and the patient has difficulty with bedside tests such as saying the months of the year backwards or counting backwards from 20. (Serial Sevens, in which seven is subtracted from 100, then from 93 and so on, is used widely by doctors but is too dependent on educational factors to be of much value [130].) Immediate and short-term memory is impaired and this results in disorientation for time. Orientation for place and person are often preserved, except in severe cases. Cognitive impairment in delirium characteristically fluctuates over time; typically, there are relatively lucid periods in the mornings with maximum disturbance at night.

Two distinct clinical subtypes of delirium can be recognized on the basis of the behaviour and alertness of the patient [95]. The agitated (or "hyperalert–hyperactive" [93]) variant of delirium is characterized by signs of sympathetic nervous system overactivity, increased alertness to stimuli and psychomotor hyperactivity. Overactivity may be purposeless and repetitive, such as plucking at bedclothes, or may involve wandering and verbal or physical aggression. In quiet (or "hypoalert–hypoactive") delirium, patients exhibit decreased responsiveness to stimuli and withdrawn behaviour. Some patients have a mixed psychomotor pattern with unpredictable swings from agitation to lethargy. Although quietly delirious patients represent half of all delirious postoperative patients [110, 176], they are likely to be missed on a busy ward unless cognitive impairment is carefully sought [97]. There is evidence that quietly delirious patients often have more severe cognitive impairment and a longer duration of hospital stay than agitated patients [95, 133]. Agitated delirium is typical of alcohol withdrawal and quiet delirium of metabolic disorders; however, most aetiological factors can lead to either variant [123, 179].

Thinking is progressively disturbed in delirium and often has a dream-like quality. Speech is rambling, illogical and incoherent, and there is impaired capacity to make judgements. Delusions occur in up to 70% of patients with postoperative delirium and are usually persecutory in nature [110]. Perceptual misidentifications and hallucinations occur chiefly at night and often result in agitated and fearful behaviour. Florid perceptual disturbances and complex delusions may be less common in the older patient [92].

Asterixis, a flapping tremor of the outstretched, hyperextended hands, is characteristic of metabolic disturbances. Multifocal myoclonus, most often in the muscles of the face and shoulders [103], and transient parietal signs such as apraxia, aphasia and agraphia are also described in delirious patients [20].

Diagnosis

Delirium is easily recognized in acutely agitated patients. A high index of suspicion is necessary to detect patients with quiet delirium. Bedside cognitive tests are useful to document changes in mental function. The Abbreviated Mental Test (AMT), which is used widely in the UK, is brief and acceptable even to sick elderly patients (table 2) [122], and a decline of 3 or more points is a sensitive and specific indicator of delirium in hospitalized medical patients [69]. Although the AMT has also been used to diagnose delirium in postoperative patients [142], the validity of the test in this group has not been evaluated to date. Recently, a brief algorithm based on the DSM-3-R criteria, the Confusion Assessment Method (CAM), has been used successfully in studying surgical patients [1, 100].

Although delirium is the commonest psychiatric syndrome in elderly postoperative patients, it is often mistaken for dementia or depression [57]. Dementia is also associated with global impairment of cognitive function and the distinction may be difficult as the two syndromes commonly coexist in elderly subjects (table 3). The most useful distinguishing feature is the pattern of onset of cognitive impairment [40, 119]. Depression is also common in physically ill elderly patients. Cognitive impairment ("pseudodementia") and withdrawn or agitated behaviour may occur in depressed patients, and mood disturbance may be a feature of delirium [92]. The distinction between the two disorders is usually straightforward, although difficulties may be ex-

Table 2 Abbreviated mental test (adapted from [36])

Each correct answer scores one point

1. Age
2. Time (to nearest hour)
3. Address for recall at end of test: 42 West Street. (Ask patient to repeat the address to ensure it has been heard correctly)
4. Year
5. Name of hospital
6. Recognition of two persons (e.g. doctor, nurse)
7. Date of birth (day and month)
8. Year of start of first world war
9. Name of monarch
10. Count backwards from 20 to 1

Table 3 Differential diagnosis of delirium and dementia

Feature	Delirium	Dementia
Onset	Acute, usually over hours to days	Gradual
Course	Fluctuating over hours	Progressive over months
Duration	Days to weeks	Months to years
Attention	Impaired, very distractable	Unimpaired, except if very severe
Orientation	Usually impaired	Often impaired
Memory	Impaired, especially short-term	Impaired, especially long-term
Perception	Disturbances common	Disturbances not common
Speech	Incoherent	Word-finding difficulties
Sleep–wake cycle	Always disrupted	Often disrupted in severe dementia

perienced during the prodromal phase of delirium. Golinger reported that 25% of surgical patients referred to a psychiatric liaison service as depressed had delirium [54].

Generalized slowing of the electroencephalographic (EEG) trace, particularly of the alpha rhythm, occurs in most patients with delirium, and the degree of slowing correlates with the severity of cognitive impairment [39]. Slowing of the alpha rhythm occurs also with increasing age and is often marked in demented patients. Alcohol and drug withdrawal states are associated with fast rather than slow EEG changes. The EEG is a useful test in patients with doubtful delirium, although in older patients and those with dementia, serial recordings may be required to confirm the diagnosis and monitor progress [90].

Incidence

There are many difficulties in interpreting studies reporting incidence rates for postoperative delirium (table 4). The incidence of postoperative delirium depends on many factors apart from the surgical procedure, including the age range and preoperative cognitive and medical status of the patient and the drugs used for premedication and anaesthesia. Diagnostic criteria are poorly defined in many

Table 4 Prospective studies of postoperative delirium. POD = Postoperative day; AMT = Abbreviated Mental Test; CAM = Confusion Assessment Method

Type of Surgery	Ref.	No. patients	Age (yr)	Delirium (% patients)	Diagnostic criteria defined	Method of ascertainment
General	[105]	100	> 64; mean 73	14	Yes	Standardized interview preop., POD 2+4
	[142]	258	> 64	10	Yes; decrease AMT ⩾ 3 pts	?
	[145]	288	> 64	7	Yes; decrease AMT ⩾ 3 pts	?
	[100]	1341	> 50	9	Yes; CAM	Standardized interview preop., POD 2–5
Cataract	[154]	27	Mean 72	8	No	Psychiatric interview POD 1+3
	[74]	1503	Mean 70	3	No	?
Hip fracture	[175]	170	> 59; mean 79	52	Yes	Daily rating by nurses POD 1–5
	[11]	59	> 64; mean 78	44	Yes; DSM-3	Standardized assessment preop., POD 1–14
	[55]	111	> 64; mean 79	61	Yes; DSM-3	Standardized assessment preop., POD 1–14
	[56]	103	> 64; mean 80	48	Yes; DSM-3	Standardized assessment preop., POD 1–14
	[111]	400	> 59	26	No	?
Joint replacement						
Hip	[65]	60	> 55; mean 71	13	No	?
Hip + knee	[128]	46	> 59	26	Yes; DSM-3	Psychiatric interview POD 4
Bilateral knee	[176]	51	Mean 68	41	Yes; DSM-3R	Standardized assessment preop., POD 1–7
Open heart						
Mixed	[60]	100	Mean 50	24	Yes	Standardized assessment preop., POD 1–7
Mixed	[164]	100	Mean 45	43	Yes	Standardized assessment preop., POD 1–discharge
Mixed	[79]	204	?	17	No	?
Mixed	[136]	50	Mean 55	72	Yes	Standardized assessment preop., POD 1–7
CABG	[16]	421	60% > 55	12	No	Clinical interview preop., POD 4
CABG	[18]	59	Mean 58	7	Yes; DSM-3	Standardized assessment preop., POD 1+6
Pulmonary thromboendarterectomy	[181]	22	Mean 49	77	Yes; DSM-3R	?

reports and few studies have used a standardized assessment for DSM criteria. Although delirium is, by definition, a fluctuating disorder and repeated assessment is necessary to ensure diagnostic accuracy, many studies involved only a single postoperative interview. Retrospective studies are particularly unreliable as recognition and documentation of delirium in the elderly by doctors and nurses is often poor [57].

In prospective studies of elderly general surgical patients, the incidence of interval delirium was found to be 7–14% [100, 105, 142, 145]. Delirium occurs in 20–40% of patients requiring intensive care admission after surgery [31, 35, 177]; patients with burns seem to be at particularly high risk [153]. The incidence of delirium after aortic aneurysm surgery was 46% in a recent prospective study [100]. Emergence reactions occur in approximately 5% of patients after general surgery [36, 60, 134]; emergence excitement may be more common in young patients and emergence somnolence in elderly patients [135]. Cataract surgery is traditionally believed to result in a high prevalence of postoperative delirium [91, 93], but recent prospective studies [74, 154] and a detailed review of the literature [154] have not confirmed this belief.

Retrospective studies suggest that delirium occurs in more than 50% of liver or lung transplant recipients [26, 67], in about 25% of heart transplant recipients [99, 118] and in 10% of renal transplant recipients [66]. Many candidates for transplantation have preoperative delirium as a result of metabolic derangements [162] and some of these patients show a dramatic improvement rather than a decline in cognitive function as a result of surgery [66].

Prospective studies using DSM criteria have consistently found high rates of delirium in patients undergoing hip fracture repair (table 4). The incidence rates after elective joint replacement are smaller but are still substantially higher than after general surgery.

Smith and Dimsdale reviewed 44 studies on postcardiotomy delirium conducted between 1963 and 1987 and reported that the rate of delirium was consistent over time at 32% [151]. However, many of these studies were retrospective and there were substantial differences in diagnostic criteria between studies. Successive studies by Heller and colleagues [60] and Kornfield, Zimberg and Malm [81] showed a reduction in the rate of delirium after valve replacement from 38% to 24% over a 5-yr period in spite of an increase in patient age and severity of illness. Although the results of two recent studies suggest that delirium is less common after coronary artery bypass grafting (CABG) than after valve surgery [16, 18], these studies did not involve daily assessment of patients. A retrospective study comparing the incidence of central nervous system (CNS) complications after CABG and valve surgery concluded that age and pre-existing disease were more important determinants of outcome than the type of cardiac surgery [84]. Non-cardiac thoracic surgery is also associated with a high risk of delirium [100, 181].

Course and prognosis

MORTALITY

In a large prospective study of patients aged 50 yr or more undergoing elective non-cardiac surgery, 4% of 117 delirious patients died compared with 0.2% of 1224 patients without delirium [100]. In a study of patients with hip fracture, the mortality rate was 39% in patients who became confused after surgery and 8% in patients who did not become confused, and this difference was attributed to the higher incidence of medical complications in the former group [111].

DURATION OF HOSPITAL STAY

The deleterious effects of postoperative delirium have been documented best in orthopaedic patients. In studies of elderly hip fracture patients, 30–40% of patients were delirious for more than 1 week [11, 55]. The prolonged duration of delirium is accompanied by prolonged stay in the acute wards, increased rate of transfer to a geriatric rehabilitation ward and subsequently to a nursing home and poorer long-term walking ability [44, 55, 175]. This poor outcome occurs in demented and non-demented patients with delirium. Although delirium is usually a more benign condition in patients undergoing elective surgery, and fewer than 20% of episodes last more than 1 week [105, 176], a two-fold increase in the duration of hospital stay and a three-fold increase in the rate of discharge to long-term or rehabilitation care has been reported in this group [100].

It is not surprising that patients who are frail, demented or have multiple, often poorly controlled, medical problems often do poorly when a postoperative complication triggers delirium. However, there is evidence that delirium itself has important consequences and that it is not only a marker of poor physical status. In a prospective study of 325 elderly patients admitted to medical and surgical wards, Levkoff and colleagues noted that delirium was associated with a three-fold increase in the duration of hospital stay and a seven-fold increase in the rate of admission to long-term care even after adjusting for pre-existing cognitive impairment, age and severity of illness [88]. Effective rehabilitation after hip repair is difficult in patients with delirium [15]. Postoperative complications including falls, pressure sores, urinary tract infections, feeding problems and aspiration pneumonia, are more common in patients with delirium after both elective and emergency surgery [11, 42, 49, 55, 100, 111]. Agitated behaviour may be disastrous in joint replacement surgery, and Boettcher reported postoperative hip displacement in four of 12 consecutive patients with delirium [14].

LONG-TERM COGNITIVE IMPAIRMENT

The most feared complication of surgery and anaesthesia in the elderly is development of permanent cognitive impairment. In 1955, Bedford reported that 7% of 250 elderly patients developed

"the grossest degree of dementia" after surgery; all of these patients had been observed by the author before surgery and were considered to be "mentally normal" [10]. A less dramatic deterioration in mental sharpness after surgery may be reported by elderly patients or their families [65, 72]. Also, permanent neuropsychological and intellectual deficits occur in up to 5% of patients after open heart surgery [140, 152, 157].

In recent years, many studies have used psychometric tests to evaluate the effects of anaesthesia and surgery on intellectual function in elderly patients. Although these tests may not detect subtle changes sufficient to concern the patient [72], the results are reassuring. In general, deterioration in performance with psychometric tests immediately after general or regional anaesthesia is followed by a return to, or even above, baseline results [6, 33, 50, 72, 129]. However, studies using psychometric tests in the postoperative period often report only grouped results and this analysis may mask considerable individual variation in the severity of impairment [64]. For example, Rollason and colleagues reported that mental function was increased above the preoperative level in 27 elderly men given a spinal anaesthetic for retropubic prostatectomy; however, two patients had significant postoperative deterioration in cognitive function which lasted more than 6 weeks [129].

While it appears that the majority of elderly people have no significant deterioration in cognitive function after an uneventful anaesthetic, there is evidence that patients who develop postoperative delirium represent a subgroup at risk for prolonged, and even permanent, cognitive impairment. Titchner and colleagues reported that 32% of 22 patients with postoperative "acute brain syndrome" failed to recover [160]. Residual organic brain damage after delirium was reported in one of seven patients who received general anaesthesia for total hip arthroplasty [65] and in eight of 67 cardiac patients who required intra-aortic balloon pump therapy [138]. In a study of elderly patients undergoing elective orthopaedic or abdominal surgery, 25% of patients with idiopathic postoperative delirium still had marked cognitive impairment 6 weeks later [76]. Recent work in medically ill patients confirmed that delirium is a less transient disorder than was previously believed. Levkoff and co-workers noted that only 4% of 125 elderly patients with delirium had recovered completely at discharge, and 80% had residual impairment 6 months later [88].

There are several possible explanations for these observations. In some patients, the aetiological factor responsible for causing delirium, such as perioperative hypoxia, may also produce structural brain damage leading to permanent cognitive impairment. In other patients, the insult triggering (auslösen) delirium is relatively mild and it seems that delirium is a marker (Kennzeichen) for diminished (vermindert) cerebral reserve or for previously unrecognized or compensated dementia. The results of Francis and Kapoor support this hypothesis; they reported that non-demented patients who developed delirium during acute medical illness experienced progressive cognitive decline during follow-up over 2 years [46]. It is not certain if an episode of delirium in itself may lead to acceleration of an existing dementing process. Beschleunigung

Pathophysiology

The pathophysiology of delirium is still poorly understood. The main theory at present is that delirium represents the clinical manifestation of diffuse, reversible impairment of cerebral oxidative metabolism and neurotransmission [90, 93]. Hence, any disease or drug interfering with neurotransmitter function or with the supply or use of substrates for metabolism can cause delirium. This mechanism would explain the relatively stereotyped nature of the response to a wide variety of physical insults and the generalized slowing of the EEG trace in most patients with delirium.

Central cholinergic pathways are involved in the regulation of attention, memory processing and sleep, and are highly sensitive to metabolic and toxic insults [93]. Gibson and co-workers suggested that impaired cholinergic neurotransmission represents the final common pathway for the development of delirium [51]. Although this hypothesis has attracted much support, it probably represents considerable oversimplification. Other neurotransmitters, notably serotonin and noradrenaline, are also important in regulating sleep and arousal and may be involved in the pathogenesis of delirium [40, 132, 170]. Understimulation and overstimulation of gamma-aminobutyric acid receptors have been implicated in the pathogenesis of benzodiazepine withdrawal delirium and hepatic encephalopathy, respectively [132]. Hypercortisolaemia and impaired beta-endorphinergic function have been reported in patients with postoperative delirium [82, 98], but the pathogenetic role of these abnormalities is unproved [114]. In conclusion, at present, we have insufficient knowledge to draw definite conclusions on the neuronal mechanism of delirium.

Although most instances of delirium are related to metabolic or toxic insults, small cerebral infarcts, especially in the right hemisphere and the subcortical nuclei, can produce an identical clinical picture [31, 43]. Mori and Yamadori have reported that frontal and basal ganglia lesions lead to quiet delirium and temporal lesions to an agitated delirium [108].

Aetiology

Postoperative delirium is usually the result of multiple factors acting synergistically [93] (table 5). In general, preoperative risk factors predispose an individual to develop delirium in the event of an intraoperative or postoperative complication, and the severity of the precipitating factor is inversely proportional to the pre-existing vulnerability of the patient.

PREDISPOSING FACTORS

Age

The risk of developing delirium after surgery increases markedly with increasing age [93].

Table 5 Causes of postoperative delirium in the elderly

Predisposing factors
Age (especially > 75 yr)
Structural brain disease (dementia, cerebrovascular disease, Parkinson's disease)
Poor medical status
Depression
Anticholinergic medications
Vitamin (especially thiamine) deficiency
Alcohol and benzodiazepine dependence
Trauma (fat embolism, brain concussion, subdural haematoma)
Epilepsy
? Anxiety
? Protein–calorie malnutrition
Precipitating factors
Medications (table 6)
Impaired cerebral oxygen supply (operative hypotension, hypoxaemia, hypocapnia or hypovolaemia)
Cardiopulmonary bypass (microemboli, total circulatory arrest time, deep hypothermia time, perfusion flow rate—pressure, ? length of time on bypass)
Infection (respiratory, urinary tract, wound, intra-abdominal, intracranial)
Metabolic disturbances (dehydration, electrolyte and acid–base imbalance, hypoglycaemia, hyperglycaemia, hypercalcaemia, hypophosphataemia, endocrine disease, hepatic, renal and respiratory failure)
Cardiac disease (heart failure, myocardial infarction)
Pulmonary embolism
Cerebrovascular disease
Seizure
Alcohol, benzodiazepine withdrawal
? Sleep deprivation
? Physical environment in intensive care unit (sensory deprivation, sensory overload, hearing and visual impairment
? Type of surgery (hip fracture, repair, open heart surgery, transplant surgery, cataract surgery)
? Length of time under anaesthesia

Seymour and Pringle noted that delirium was three times more common in patients aged 75 yr and older than in patients aged 65–75 yr [142]. Preoperative medical fitness and increased prevalence of disease in older people are more important determinants of delirium than age itself [143, 145]. Nevertheless, multivariate analysis confirms that chronological age and the effects of "normal ageing" are also significant [55, 100]. Elderly people have a reduced capacity for homeostatic regulation in the face of stresses such as those imposed by surgery and anaesthesia, and age-related changes in brain neurochemistry and drug metabolism increase the likelihood of drug side effects.

Preoperative medical problems

In a prospective study from Cardiff, 80% of 290 elderly patients presenting for surgery had at least one, and 30% had three or more preoperative medical problems; delirium and other postoperative complications were commonest in patients with multiple problems [145]. Another study identified severe physical impairment and markedly abnormal electrolyte concentrations as independent predictors of delirium in surgical patients [100]. Patients with cancer also have a high risk of developing postoperative delirium, but the mechanism is not clear [148].

Structural brain disease

Dementia and cerebrovascular disease greatly increase the risk of developing delirium [8, 100, 109]. In studies of patients with hip fractures, pre-existing cognitive impairment was the most important factor predicting delirium after surgery [55]. A recent report also identified a high risk of postoperative delirium in patients with Parkinson's disease [53]; this risk could not be attributed to treatment with dopaminergic or anticholinergic medications.

Trauma

Fat embolism is a potential cause of delirium in orthopaedic patients who have fractures of long bones or surgery involving reaming of the bone marrow: manifestations include hypoxaemia, fever, thrombocytopenia and delirium [75, 176]. Delirium is also a consequence of traumatic asphyxia, cerebral concussion and contusions, and subdural haematoma [104].

Nutritional deficiency

Protein–calorie malnutrition and vitamin deficiencies are common in elderly subjects, especially in those living in nursing homes [87]. Although it seems probable that nutritional deficiency increases the risk of postoperative delirium [163], only thiamine deficiency has received much attention. Postmortem studies suggest that Wernicke–Korsakoff syndrome caused by thiamine deficiency is missed frequently in non-alcoholic patients, in part because the classical triad of delirium, ataxia and ocular signs is uncommon and many patients have only delirium [58]. Thiamine deficiency has been implicated as a cause of delirium in patients with hip fracture [116]. Low preoperative serum albumin concentration is associated with a high risk of postoperative delirium [126]; however, hypoalbuminaemia is chiefly a marker of serious illness rather than an indicator of nutritional status [47].

Psychological factors

The role of preoperative anxiety in the pathogenesis of delirium is uncertain. Morse and Litin reported that patients who were worried about dying were 10 times more likely to become delirious than patients without such fears [109]. However, a prospective study in orthopaedic patients found no relationship between preoperative anxiety and later delirium [150]. Indeed, it has been suggested that a moderate amount of anxiety before surgery helps postoperative recovery [182].

There is no doubt that depressed patients are more likely to develop delirium [11, 109]. Much of the blame has been attributed to treatment with antidepressant drugs with anticholinergic activity [11]. However, it is now known that structural subcortical lesions, probably secondary to small strokes, are common in elderly patients with depression and these lesions increase the risk of delirium [43].

Table 6 Medications associated with delirium (derived from [89, 92, 110, 132, 152, 158, 165])

- Drugs with central anticholinergic activity
  - Belladonna alkaloids
  - Tricyclic antidepressants
  - Neuroleptics
  - Antiparkinsonian agents
  - Antiarrhythmics
  - Benzodiazepines
  - Opioids
  - Ketamine
  - Halogenated anaesthetic agents
- Cardiovascular agents
  - Digoxin
  - Beta-blockers
  - Diuretics
  - Calcium channel blockers
- Anticonvulsants
- Anti-inflammatory agents
  - Corticosteroids
  - Non-steroidal agents
  - Cyclosporin
  - OKT3
- Gastrointestinal agents
  - H_2 blockers
  - Metoclopramide
- Antibiotics
  - Penicillin
  - Ciprofloxacin
  - Gentamicin
  - Cephalosporins
- Oral hypoglycaemics

PRECIPITATING FACTORS

The most important operative factors promoting delirium are the use of deliriogenic drugs and impairment of cerebral oxygen supply. There is no difference in the incidence of delirium after regional or general anaesthesia when both techniques are performed expertly. This is contrary to the suggestion by Hole, Terjesen and Breivik that regional anaesthesia was less likely to cause delirium [65]; they diagnosed delirium in none of 29 patients receiving extradural anaesthesia and in seven of 31 patients after general anaesthesia for hip replacement. However, standardized criteria and mental tests were not used in this study and comparison between the techniques was not blinded. Studies using blinded assessments and formal mental tests have failed to demonstrate any difference between the two techniques in the incidence of delirium [11, 22, 55] or, except during the first 24 h after surgery, in the results of psychometric tests [22, 23, 33, 72, 73, 113, 127].

The risk of delirium increases with the complexity of the surgical procedure [109]. However, it is not clear if this is caused by the often poor medical condition of patients requiring major surgery or the metabolic stress of surgery itself. The failure of regional anaesthesia, which ameliorates the metabolic response to surgery [173], to reduce the incidence of delirium argues against a major role for this factor.

It is dangerous to assume that postoperative delirium is entirely caused by the effects of surgery or anaesthesia. In studies of delirious general surgical patients, postoperative medical or surgical complications were identified as responsible in 90% of cases [105, 111, 160]. Even when delirium develops after cardiopulmonary bypass, a potentially reversible cause can be found in most patients [16]. The commonest precipitants of delirium are hypoxaemia, chest infections, metabolic disturbances, vascular disease, drug toxicity and alcohol withdrawal [165]. The role of sleep deprivation and environmental factors is less clear cut, and both may be facilitating rather than precipitating factors. Pain and urinary retention are important causes of restlessness on emergence from anaesthesia and also cause interval delirium [13, 93].

Medications

Almost any drug can cause delirium (table 6). Drugs given during the preoperative, operative and postoperative periods can have an additive effect in the elderly surgical patient.

Anticholinergic medications. Many drugs used in the operative and postoperative period are known to have central anticholinergic actions (table 6) [93, 112, 135, 155, 168]. Furthermore, radioceptor assays have identified significant antimuscarinic activity in many other commonly prescribed agents, including histamine$_2$ receptor (H_2) blockers, corticosteroids and digoxin [166].

Drugs with central anticholinergic actions are responsible for a large proportion of emergence actions [135] and can also cause interval delirium [11, 55, 167]. The risk of delirium increases as a function of the number of medications with additive effects on cholinergic neurotransmission; Tune and colleagues reported an association between postcardiotomy delirium and increased serum anticholinergic activity, measured 24 h after cardiac surgery [169]. Pyrexia, sleep loss and pain further increase the risk of delirium in patients given anticholinergic agents [93]. Signs of peripheral antimuscarinic activity are present in some, but not all, patients with central anticholinergic toxicity.

In general, central cholinergic neurotransmission is impaired in later life, especially in patients with Alzheimer's disease [51]. Hence, it is not surprising that elderly patients are very susceptible to the central effects of anticholinergics; even low concentration atropine eyedrops can cause delirium after cataract surgery [21, 154]. Hyoscine is particularly deliriogenic and should be avoided in elderly patients [137]. A reduction in the incidence of delirium has been reported with the decline in the use of atropine for premedication [147].

Opioids. Opioid analgesics have been linked to the development of delirium in several studies [46, 105], although there is evidence that opioids are not a risk factor for delirium in patients with few preoperative medical problems [176]. Elderly people are more sensitive to the CNS effects of opioids. Also, the effects of opioids on respiratory function may exacerbate hypoxaemia and prolong delirium in postoperative patients [93].

intra-aortic balloon pump therapy for cardiogenic shock, administration of high-dose opioid infusions to manage agitation was associated with a high risk of permanent organic brain damage [138]; however, it is difficult to draw definite conclusions in view of the retrospective nature of this study. In a randomized trial, "significant confusion" occurred in 18% of patients given i.m. morphine for postoperative pain and 2% of patients given a similar dose via patient-controlled analgesia, and the authors attributed this difference to higher peak concentrations of morphine in the first group [37]. The most deliriogenic opioid is pethidine, possibly because of the anticholinergic activity of its active metabolite, norpethidine [106].

Other medications. Of the i.v. anaesthetic agents, ketamine and, less frequently, etomidate, can produce emergence delirium [77, 125]. Ketamine characteristically produces vivid hallucinations and nightmares, and perceptual disturbances can persist for 24 h. Prominent hallucinations also occur in delirium caused by lignocaine toxicity [139]. A characteristic feeling of impending doom was described in cardiac patients receiving i.v. lignocaine, but this may also occur when lignocaine is used for regional or local anaesthesia [139].

Although elderly patients are more sensitive to the cerebral and cardiovascular effects of the volatile and inhalation anaesthetic agents, and residual effects of these agents on psychometric tests can last for up to 1 week [27, 63], there is little evidence that these agents cause delirium. It has been suggested that nitrous oxide might be involved in the development of delirium, either by interfering with vitamin B_{12} metabolism or by inducing deafness [32], but there is no evidence to support these hypotheses.

Drug toxicity is particularly important in intensive care patients, many of whom receive multiple deliriogenic agents. Delirium caused by H_2 blockers is not dose-related and, contrary to earlier reports, there is no evidence that any one H_2 blocker is more liable to produce delirium [19]. Delirium caused by corticosteroids is dose-related and the risk is much greater with doses greater than prednisolone 40 mg or its equivalent daily [180]. Delirium caused by high-dose steroids is especially common in transplant patients and these patients are also prone to develop dose-dependent delirium during treatment with cyclosporin [29]. Delirium is an early sign of digoxin toxicity in the older patient [93]. Antibiotics are also a significant but often neglected cause of delirium [161].

Impaired cerebral oxygen supply

Impaired autonomic responsiveness with ageing, and the high prevalence of cardiovascular, cerebrovascular and respiratory disease render the elderly patient more vulnerable to brain hypoxia as a consequence of perioperative instability. While severe hypoxaemia or hypotension may lead to death or permanent brain damage, more moderate changes may manifest as delayed recovery after surgery or interval delirium.

Elderly people, especially those with structural brain damage, may be sensitive to the cognitive effects of mild to moderate hypoxaemia [52]. Arterial oxygen tensions are lower after general anaesthesia than after regional anaesthesia, and Berggren and colleagues noted an association between hypoxaemia just after surgery and subsequent delirium in patients with hip fracture who had general anaesthesia [11]. Hypothermia and postoperative shivering may contribute to early hypoxaemia [32] and surgical stress itself may increase cerebral oxygen demand [131]. Hypoxaemia, which can last several days, is also common in the later postoperative period, particularly during sleep and after administration of opioids [71]. Rosenberg and Kehlet reported that hypoxaemia, detected by pulse oximetry on the second postoperative night, is the most important risk factor for decline in mental test score after major abdominal surgery [131] and for the development of delirium after thoracotomy [1]. Other workers have reported similar findings [83].

Regional anaesthesia is associated with a greater decrease in arterial pressure than general anaesthesia. In one study in patients with hip fracture, delirium developed in 12 (92%) of 13 patients receiving regional anaesthesia whose systolic arterial pressure decreased to 80 mm Hg or less [55]. Subsequent studies have confirmed the importance of hypotension during regional anaesthesia as a risk factor for delirium [56]. Hypocapnia produced by excessive passive hyperventilation also decreases cerebral blood flow, and the combination of hypocapnia and hypotension is particularly threatening to the cerebral oxygen supply [32].

Cardiopulmonary bypass

Neurological impairment after cardiac surgery may be related to a reduction in cerebral perfusion pressure below the autoregulatory threshold or to focal occlusion of cerebral vessels by emboli. Intraoperative transcranial Doppler techniques have identified a high frequency of microemboli to the brain, especially during aortic instrumentation [120]. The significant correlation between the number of microemboli and neuropsychological function after bypass suggests that focal ischaemia may be responsible for a large proportion of cerebral dysfunction after cardiac surgery [101]. In general, the severity of heart disease and the complexity of operation correlate with the incidence of delirium [34, 60]. Conflicting reports have appeared on the role of deep hypothermia, duration of bypass, duration of anaesthesia, and perfusion flow rate or pressure in the pathogenesis of delirium [34, 60, 151]. A recent study reported delirium in 77% of patients undergoing pulmonary thromboendarterectomy, a procedure which requires much longer periods on bypass than CABG or valve replacement, and in this population there was a clear relationship between delirium and total circulatory arrest and deep hypothermia times [181]. Discriminant analysis in another prospective study identified arterial pressure during CPB, age and temperature on the third day after surgery as the only independent predictors of delirium [136].

Infectious and metabolic insults

Chest infections develop after surgery in about 20% of elderly patients and account for up to 25% of potentially preventable postoperative deaths in this age group [144]. Early diagnosis and treatment is essential but may be difficult as typical features such as cough, purulent sputum, pyrexia and elevated white cell count may be absent. Delirium is a common presenting feature of chest infections in the elderly and may precede the development of physical or radiographic signs [104]. Urinary tract, wound, intra-abdominal and intracranial infections may also present with delirium [90, 161].

Many metabolic disturbances may cause delirium (table 5) [90]. Delirium is both a consequence and a cause of dehydration and hyponatraemia. Clinical diagnosis of dehydration may be difficult in elderly patients and a high index of suspicion is required [146]. Hyponatraemia, which is usually mild and transient, is common in the postoperative period as a result of the antidiuresis produced by the stress of surgery [44]. Severe hyponatraemia can result from the administration of large quantities of 5% glucose or, during transurethral resection of the prostate, from absorption of hypotonic irrigating fluid. In general, cerebral effects of hyponatraemia are rare unless the serum sodium concentration is less than 125 mmol litre^{-1} and has decreased rapidly. However, elderly patients and those with brain disease, alcoholism or poor nutritional status may be vulnerable with less extreme changes [171], and a preoperative sodium concentration less than 130 mmol litre^{-1} or greater than 150 mmol litre^{-1} is a strong independent predictor of postoperative delirium [100].

* verminderter Natriumgehalt im Blut

Vascular disease

Postoperative myocardial infarction occurs in approximately 2% of elderly patients [146]. Typical chest pain is uncommon in this age group and delirium is a common presentation [9]. Pulmonary embolism can also present as a change in mental status. Major strokes occur in about 1% of general surgical patients [146] and delirium is prominent in about 10% of these patients. Small localized strokes are probably more common and many present only with delirium [90]. Seizures can result from a stroke or from acute metabolic disturbance or drug toxicity. Postictal delirium can last for several days and diagnosis is difficult if convulsions are absent or not witnessed [104, 121].

Alcohol and benzodiazepine withdrawal

Alcohol abuse is not uncommon in elderly patients and may be successfully hidden from carers and doctors [17]. Benzodiazepines are among the most commonly prescribed drugs in elderly people [45]. Symptoms caused by withdrawal usually occur between 12 and 72 h after sudden cessation of the drug or alcohol but may be delayed, especially in older patients receiving long-acting benzodiazepines. Although Lipowski suggests that withdrawal symptoms are most likely in patients with a daily intake of 1 pint of whisky or its equivalent for 10 of 14 days before admission [93], a considerably lower intake of alcohol may be significant in older patients. In a recent study of elderly patients, a history of alcohol use greater than 3 units a week before surgery was associated with a two-fold increase in the incidence of delirium, and alcohol intake was a significant predictor of delirium on multivariate analysis [176]. Although agitation is typical of withdrawal syndromes, quiet delirium can also occur [140]. Alcoholism is particularly common in patients operated on for oral and laryngopharyngeal cancer [62]. Vitamin deficiency, especially thiamine, hepatic failure and chronic subdural haematoma should also be considered in delirious alcoholic patients.

Sensory deprivation or overload

The presence of a lucid interval before the onset of postoperative delirium is consistent with a role for environmental factors in the pathogenesis of the disorder [80]. Visual and hearing impairment are risk factors for delirium in hospitalized elderly medical patients [68]. Sensory overload caused by noise and constant lighting in the surgical intensive care unit has been proposed as a possible precipitant of delirium [35]. Other authors have emphasized the importance of sensory deprivation caused by factors such as water beds and immobilization by monitoring equipment in intensive care units and failure to wear spectacles and hearing aids [174]. Wilson reported that delirium occurred in 40% of patients in a windowless intensive care unit and in 20% of patients in a unit possessing windows [177], but other workers failed to confirm this finding [105]. May, Ehleben and DeClement reported that delirium developed in 40% of burn patients treated in special isolation units and in 7% of matched patients treated in standard cubicles [102]; multivariate analysis suggested that the combination of isolation and organic factors (hypoxia, burn size and sepsis) was responsible for delirium in most patients. Patching of the eyes has been blamed in the past for delirium after cataract extraction ("black patch delirium") [154]. However, there is little evidence to support this hypothesis, and removal of the patch from the unoperated eye usually fails to produce any improvement in symptoms [90].

In conclusion, the evidence at present on the role of environmental factors and sensory deprivation in the pathogenesis of delirium is inconclusive, but it seems likely that physical factors may facilitate the development of delirium in susceptible patients.

Sleep deprivation

Rapid eye movement (REM) sleep is important for normal mental function. Severe sleep disturbance, with suppression of REM sleep, has been noted after cardiac [70] and non-cardiac surgery [38]. Aurell and Elmqvist suggested that this represented abnormality of the sleep–wake regulating system rather than a reaction to environmental disturbance [7]. A

study of patients who underwent cardiac surgery found that cognitive impairment correlated with sleep loss on the day after delirium developed but not on the preceding day [59]. This suggests that sleep loss is a result of, rather than a cause of, delirium.

Management

Successful management of the patient with delirium requires early diagnosis and investigation, and treatment of the underlying causes. Fluid and electrolyte balance and nutrition should be maintained during the delirious episode and psychological support is essential. Pharmacological treatment is required in a minority of patients to prevent self-injury and control distress. Physical restraints are inhumane, increase agitation and may even increase mortality [41].

INVESTIGATION AND TREATMENT OF THE UNDERLYING CAUSE

A careful search for precipitating organic factors is indicated in all delirious patients [109, 111]. Carers should be asked about the use of alcohol and benzodiazepines and previous cognitive function. Clinical evaluation should include assessment of hydration and nutritional status, examination for urinary retention or constipation, and of cardiovascular and neurological status, and a search for possible sites of infection. The medication chart should be inspected and recent changes noted. Initial tests include serum urea, glucose and electrolytes concentrations, liver function tests, arterial blood-gas analyses, blood count, urine, blood and possibly sputum cultures, electrocardiography and chest x-ray. In difficult cases, CT brain scan, EEG and lumbar puncture may be required. Aakerlund and Rosenberg have demonstrated the importance of detecting and treating nocturnal hypoxaemia in delirious patients, and supplementary oxygen should probably be considered in all delirious patients [1].

SUPPORTIVE MEASURES

Delirious patients are liable to become dehydrated and this may prolong or exacerbate cognitive impairment [78]. I.v. therapy is clearly indicated in the shocked or severely dehydrated patient; s.c. fluids are a useful alternative in agitated patients when dehydration is less severe or when maintenance fluids are indicated [94]. Patients with borderline nutritional status may deplete their stores of B complex vitamins during severe illness [116]. Although there is no proof at present that they shorten the duration or severity of delirium, multivitamin supplements should probably be given to all delirious patients [30, 115].

Fear and anxiety are the dominant emotions in delirious patients, even in those who appear listless and withdrawn. Frequent reassurance and explanation is necessary, especially if invasive procedures are contemplated. It is often recommended that delirious patients should be nursed in a well-lit room [93], but there is no evidence to support this, and it may be preferable to maintain the semblance of a day–night cycle by dimming lights at night. Noise from alarms and equipment should be minimized. Family visits should be encouraged as they may reduce anxiety and promote orientation.

PHARMACOLOGICAL TREATMENT

Sedation is a double-edged weapon in the management of delirium. While sedative medications may be essential in the agitated, hallucinating patient, it is easy to oversedate and to prolong delirium, especially in those patients who fluctuate between agitation and lethargy [89].

Sedatives should be started at low doses and prescribed as regular medication for short periods, rather than given intermittently in high doses. The likely aetiology of the delirium must be taken into account in choosing appropriate therapy for agitation. In most cases, neuroleptic medications are the drugs of choice [90]. They do not impair respiratory function and are less likely to aggravate cognitive impairment than benzodiazepines. Thioridazine is used widely, but it has significant anticholinergic and cardiovascular effects and can accumulate in the elderly [96]. Haloperidol is probably the best choice, although few direct comparisons with other agents have been reported. Oral haloperidol in an initial dose of 0.5–2.0 mg, three or four times daily, is usually adequate for elderly patients [93]. More rapid treatment is sometimes needed in intensive care patients to prevent injury. Haloperidol i.m. is generally safe and effective, although absorption is sometimes erratic and the discomfort of an injection may aggravate agitation. Haloperidol i.v. has been used widely in the intensive care setting, although its use in this manner is not licensed in the UK; in elderly patients, the starting dose is 0.5–2.0 mg for mild agitation and 5–10 mg for severe agitation [158]. If agitation persists, the previous dose should be doubled every 20 min until agitation subsides.

Extrapyramidal symptoms are the main side effects of treatment with haloperidol, but these are uncommon with i.v. haloperidol, and the rate is reduced further in patients given both i.v. benzodiazepines and haloperidol [103]. Torsade de pointes is a rare complication of i.v. haloperidol and occurs mainly in patients with prolonged Q-T intervals [178].

Benzodiazepines are the treatment of choice for alcohol and benzodiazepine withdrawal and for patients with extrapyramidal disease. However, they worsen respiratory depression and can cause paradoxical excitement. Lorazepam and temazepam, which have relatively short half-lives, are usually preferred; the former is available for parenteral use. Midazolam has been used for i.v. sedation in delirious intensive care patients, but the half-life is prolonged in the elderly and seriously ill patient; propofol may be a useful alternative for short-term i.v. treatment of severe agitation in the intensive care unit [2]. Chlormethiazole is a useful alternative for treating alcohol withdrawal and other forms of delirium in the elderly [48]; it may be necessary to add electrolytes to the i.v. preparation as this contains only 32 mmol litre^{-1} of sodium.

Physostigmine can rapidly reverse delirium caused by anticholinergic agents [135]. In elderly patients, a dose of 0.5 mg is given by slow i.v. injection; this can be repeated at intervals of 10–20 min to a total of 2 mg [93]. Although physostigmine may be of diagnostic value, the therapeutic effect is short-lived, and the long list of relative contraindications, including ischaemic heart disease, chronic airways disease, mechanical bowel or bladder obstruction, and peptic ulcer disease limit its value in elderly patients.

Prevention

Prevention of delirium requires close co-operation between medical, surgical, anaesthetic and nursing staff. Two studies have compared the incidence of postoperative delirium in patients with hip fracture before and after a series of interventions based on changing risk factors. Gustafson and colleagues reported that a joint geriatric–anaesthetic approach reduced the incidence of delirium from 61% to 48% [56]. Furthermore, episodes of delirium in the intervention group were milder and of shorter duration than those in the control group, and the mean duration of stay on the orthopaedic ward was reduced from 17 to 12 days. Interventions consisted of pre- and postoperative geriatric assessment, oxygen therapy during surgery and, for the first postoperative day, prevention and treatment of perioperative hypotension and early detection and treatment of postoperative complications. Williams and colleagues reported that nursing interventions to minimize environmental stress reduced the incidence of acute confusion in elderly patients with hip fracture from 52% in a previous study to 44% in the intervention group [174]. A combination of medical and nursing measures might be even more effective.

PREOPERATIVE MEASURES

It is essential to optimize medical condition before surgery whenever possible. Metabolic disturbances, hypoxia, dehydration, heart failure and infection should be treated aggressively. Mullen and Mullen noted a reduction in mortality with vigorous monitoring and treatment of urinary tract infections before hip fracture repair [111]. Even if remediable risk factors are absent, preoperative identification of patients at high risk of developing delirium and other complications encourages careful management and close postoperative surveillance [100]. Simple bedside cognitive tests should be performed before operation in all elderly patients to identify those with cognitive impairment and to provide a baseline for assessing changes in the postoperative period; if the purpose of testing is explained carefully, few patients take offence. ubl

Prophylactic multivitamin supplements have been advocated for patients with hip fractures [116]. However, a randomized, double-blind trial found no reduction in the incidence of postoperative delirium with supplementation [28]; the authors of this study recommended that prophylactic vitamins should be restricted to alcoholic or obviously malnourished patients.

Preoperative explanation and discussion by the anaesthetist can reduce the need for postoperative analgesia [124, 184]. It is probably wise to warn potentially vulnerable patients about the possibility of transient confusion after surgery even though the benefits of this practice are unproved [85, 86, 141, 156].

ANAESTHETIC MEASURES

Prevention and treatment of perioperative hypoxia and hypotension are of paramount importance [56]. Invasive monitoring is required in selected patients. Other patients may benefit from the current practice of monitoring for perioperative hypoxaemia by pulse oximetry, even though the only randomized trial of this approach (albeit in patients with a median age of 55 yr) found no diminution in postoperative cognitive impairment in patients monitored by pulse oximetry, in spite of an increase in the detection and treatment of hypoxaemia in the monitored group [107]. The use of peripherally active anticholinergics, such as glycopyrronium instead of atropine, is of proven benefit in reducing the incidence of postoperative delirium [3, 135, 147].

POSTOPERATIVE MEASURES

Early recognition and treatment of medical and surgical complications may prevent the development of delirium [90]. Further research is needed to assess the value of prolonged postoperative oxygen therapy and of nutritional support for selected patients. Williams and colleagues reported the benefits of "interpersonal and nursing interventions" in preventing delirium [174]. They believe that repeated orientation and explanation, ensuring that spectacles and hearing aids were worn, and improved continuity of care were the key factors in this success. Further research is necessary to confirm these findings.

Conclusions

Although delirium is a common and important complication in the elderly postoperative patient, it has been relatively neglected by researchers, and few prospective studies using standardized criteria have been conducted. Delirium occurs in at least 10% of elderly general surgical patients and in up to 50% of patients undergoing hip fracture repair. The aetiology is multifactorial: advanced age, cerebral damage and poor preoperative medical status are important predisposing factors; infection, anticholinergic drugs and causes of impaired cerebral blood supply are the best established organic precipitants of postoperative delirium. The aetiological significance of sensory deprivation, psychological stress and nutritional deficiencies is uncertain at present and requires further research. Delirium is associated with a prolonged hospital stay in surgical patients and this is at least partly attributable to delirium itself rather than to the underlying physical illness. In some patients, delirium presages permanent cognitive impairment. Management of de-

lirium requires vigorous treatment of reversible causes and supportive measures to minimize the consequences of acute confusion; sedative medications are usually not required. There is evidence that meticulous medical care and nursing interventions to maintain orientation can reduce the incidence of delirium. Further advances in the treatment and prevention of delirium require improved knowledge of the pathogenetic mechanisms underlying the disorder.

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